may not be relevant to clinical maintenance strategies and may lead to erroneous conclusions regarding risk to the pregnant addict or her child. Furthermore, withdrawal in utero rather than continuous opiate exposure may be responsible for many of the detrimental sequelae reported for this class of drugs.

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16. Although weight loss was no greater in the 4LNx group, additional signs of withdrawal, such as hyperirritability, wet-dog shakes, and rhinorrhea were observed, indicating that withdrawal was more severe in this group than in the 1LNx group.
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19. The data in Fig. 1 represent the average for males and females since sex distribution was approximately equal for all groups and since no sex differences in these measures were observed at birth. The data were analyzed by analysis of variance with litters, rather than individual pups, being used as the experimental unit. Duncan's new multiple range test was used to compare individual treatment means at a significance level of $P < .05$.
20. This research, supported by PHS grant DA 01880, was presented in brief at the annual meeting of the American Society of Pharmacology and Experimental Therapeutics, August 1980.

2 September 1980; revised 12 January 1981

Prenatal Withdrawal from Opiates Interferes with Hatching of Otherwise Viable Chick Fetuses

Abstract. *Fetal chicks were made opiate-dependent by injections of* N-*desmethyl*-l-α-*acetylmethadol into the chorioallantois on day 3 of embryogenesis. The injections had no effect on subsequent hatchability; however, spontaneous fetal motility was significantly depressed. Injection of naloxone caused a significant increase in the motility of the opiate-exposed fetuses but had no effect on control fetuses. That naloxone's effect was an expression of opiate withdrawal and not due to antagonism of depressed motility is also supported by the observation that naloxone significantly reduced the hatchability of opiate-exposed chicks and not of control chicks. Thus the withdrawal of a developing organism from a narcotic may be more deleterious to its survival than continued exposure.*

Both the effects of maternal narcotic addiction on the newborn infant and the neonatal narcotic withdrawal syndrome have been subjects of extensive discussion (*1–4*). Although the diagnosis of withdrawal is often difficult to make, approximately 85 percent of infants born to addicted women show some signs of withdrawal (*3, 4*). Less information is available concerning fetal withdrawal, which may present as great a threat to the fetus and neonate as does postnatal withdrawal to the neonate. Fetal withdrawal, as evidenced by an increase in fetal motility and a high incidence of placental staining by meconium (*3, 5*), may or may not be coincident with maternal withdrawal. However, maternal withdrawal may itself exacerbate the effects of fetal withdrawal (*3, 5*). The possibility of fetal distress due to withdrawal and of abortion or premature labor have prompted some clinicians to recommend maintaining pregnant addicts on low doses of methadone. Others, in view of the apparent toxic effects of opiate exposure (*6*), encourage a drug-free state during pregnancy or try to gradually reduce the doses to the lowest possible level before delivery.

We sought to determine whether the effects of an opiate are less detrimental to normal fetal development than withdrawal precipitated by naloxone. Several reports have described adverse consequences of fetal exposure to opiates (*7*); some of these effects may be attributed to a direct action on the developing fetus. However, many of these sequelae may be secondary consequences of in utero withdrawal [resulting from inappropriate dosing schedules (*8*) in species that rapidly metabolize or excrete opiates]. By using chick fetuses, we were able to examine the direct effects of opiates on a developing organism in the absence of the maternal-fetal interaction present in viviparous species (*9*). The opiate used was *N*-desmethyl-*l*-α-acetylmethadol (NLAAM) (*10*), a long-acting substance. By using NLAAM in lieu of the parent compound, we did not have to rely on the immature metabolizing capabilities of the chick embryo to ensure its exposure to the most potent metabolite, which is probably responsible for most of the pharmacological effects in animals and man (*10*).

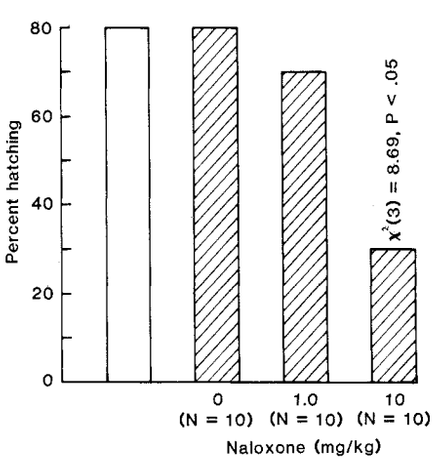

Fig. 1. Effect of naloxone on hatchability of chick fetuses exposed to propylene glycol or NLAAM. The open bar represents the hatchability of vehicle-treated fetuses given saline or naloxone on the 19th day of incubation ($N = 30$). The shaded bars represent the hatchability of fetuses treated with NLAAM (2.5 mg/kg) and given saline or naloxone on day 19.

Fertile eggs of a White Leghorn strain were obtained from a local hatchery, randomly assigned to vehicle or drug treatment groups, and placed in a rotating forced-air incubator maintained at 38°C and 58 percent relative humidity. On the third day of incubation, 30 μl of vehicle (50 percent propylene glycol) or NLAAM (2.5 or 3.4 mg per kilogram of egg) was injected into the chorioallantois (*11*).

In the first experiment we determined whether naloxone affects the hatchability of fetuses treated with NLAAM. On the 19th day of incubation, the chorioallantois of eggs treated with vehicle or NLAAM (2.5 mg/kg) was injected with 0.9 percent saline or naloxone (1.0 or 10

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mg/kg). Hatchability was determined on days 21 to 22. Neither dose of naloxone affected the hatchability of the eggs that had been treated with propylene glycol, and these groups were pooled with the saline group. Naloxone (10 mg/kg) significantly reduced the hatchability of NLAAM-exposed fetuses; treatment with NLAAM alone had no effect (Fig. 1).

Administration of naloxone to NLAAM-treated fetuses may precipitate a withdrawal state incompatible with normal hatching. To explore this, we monitored the movements of 19-day-old fetuses that had been treated with vehicle or NLAAM (3.4 mg/kg) and observed the response to naloxone. Platinum electrodes were inserted 3 mm into each of two holes drilled approximately 180° apart midway along the longitudinal axis of the egg (*12, 13*). The electrodes were connected to a polygraph recorder. During the recording sessions, the eggs were kept in a forced-air incubator maintained at 36° to 37°C. Normally, bursts of chick fetal movement are interspersed with periods of relative quiescence (*13*). During a 2-minute recording session before naloxone was injected into the chorioallantois, normal levels of motility were seen in the vehicle-treated fetuses and a significant reduction in motility was observed in the NLAAM-exposed fetuses (Fig. 2 and Table 1). Injection of naloxone (1.7 mg/kg) 2 minutes before a second 2-minute session reversed the narcotic's effect on motility. A higher dose of naloxone (5 mg/kg), which had no effect on the motility of vehicle-exposed fetuses, caused a significant increase in motility in the NLAAM-exposed fetuses (Fig. 2 and Table 1). These data, together with the data on hatchability, indicate that a single injection of an otherwise nontoxic dose of NLAAM on the third day of incubation can induce a state of dependence in the fetal chick during the perinatal period. The depressed motility of the NLAAM-exposed fetuses is consistent with findings by Kirby (*14*), who reported that the motility of rat fetuses is reduced by morphine—an effect reversed by naloxone.

Hatching behavior comprises a series of complex, coordinated movements leading to attainment of the normal hatching position (*13, 15, 16*). If the fetus is not properly positioned, the chances of successful hatching are greatly reduced (*15*). Our results suggest that the reduced hatchability of NLAAM-treated chick fetuses challenged with naloxone may be related to an increase in motility caused by withdrawal. Our results are in accordance with those of Cohen *et al.* (*17*), who demonstrated withdrawal in morphine-dependent lamb fetuses after the direct administration of naloxone; withdrawal was evidenced by fetal cardiovascular changes and the presence of meconium in the amniotic fluid. Furthermore, our results complement findings of Lichtblau and Sparber (*18*), who reported that naloxone-precipitated withdrawal in pregnant rats dependent on *l*-α-acetyl-methadol results in an increase in stillbirths and diminished pup size and weight at birth, effects not observed in pups prenatally exposed to the compound in the absence of naloxone.

Although the rat studies indicate that the congenital effects of prenatal withdrawal may be more deleterious than the effects of continued exposure at maintenance levels, the maternal-fetal interactions have precluded any definite conclusions. The present study, however, excluded maternal influences.

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Table 1. Effect of naloxone on the motility of 19-day-old chick fetuses exposed to vehicle or NLAAM on day 3 of embryogenesis. The baseline motility of the fetuses was recorded for 2 minutes. They were then exposed to naloxone at 1.7 or 5.0 mg/kg, and 2-minute records were made 2 minutes later.

Treatment	Motility score*		
	Before naloxone	After naloxone	
		1.7 mg/kg	5.0 mg/kg
Vehicle	18.3 ± 1.3 (N = 20)	23.0 ± 3.5 (N = 10)	19.4 ± 4.6 (N = 10)
NLAAM (3.4 mg/kg)	9.9† ± 1.3 (N = 20)	20.9 ± 4.5 (N = 10)	29.7 ± 3.2† (N = 10)

*Number of epochs (for definition of epoch, see legend to Fig. 2). †Significantly different from control values at $P < .05$ (Student's t-test).

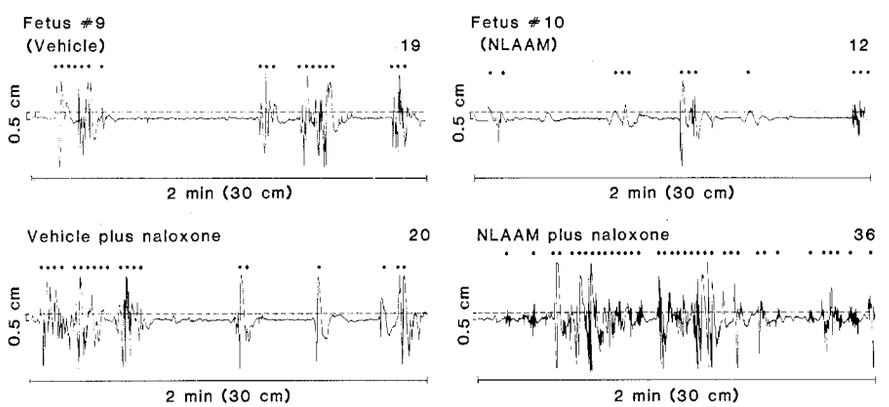

Fig. 2. Examples of spontaneous and naloxone-induced motility in two 19-day-old chick fetuses exposed to propylene glycol or NLAAM (3.4 mg/kg) on day 3 of embryogenesis. Points above pen deflections indicate epochs of movement—2-second segments (0.5 cm) of pen deflections at least one of which was higher than 0.5 cm (dashed line) on chart paper (Gilson P-111) moving at 15 cm/min.

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19. Supported in part by PHS grant DA01880. A brief presentation of this work was made at the annual meeting of the American Society for Pharmacology and Experimental Therapeutics, Rochester, Minn., August 1980.
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2 September 1980, revised 12 January 1981

Speech Perception Without Traditional Speech Cues

Abstract. *A three-tone sinusoidal replica of a naturally produced utterance was identified by listeners, despite the readily apparent unnatural speech quality of the signal. The time-varying properties of these highly artificial acoustic signals are apparently sufficient to support perception of the linguistic message in the absence of traditional acoustic cues for phonetic segments.*

A person listening to a continuously changing natural speech signal perceives a sequence of linguistic elements. Researchers have attempted to characterize this perceptual process by analyzing the acoustic properties of speech signals that specify the linguistic content (*1*). In the present study, however, listeners perceived linguistic significance in acoustic patterns with properties differing substantially from those traditionally held to underlie speech perception. And, although listeners accurately reported the linguistic content of these acoustic patterns, the signal was also perceived, simultaneously, not to be speech. These novel findings imply that the process of speech perception makes use of time-varying acoustic properties that are more abstract than the spectra and speech cues typically studied in speech research (*1*).

The stimuli used in our study consisted of time-varying sinusoidal patterns that followed the changing formant center frequencies (the natural resonances of the supralaryngeal vocal tract) of a naturally produced utterance. The sentence "Where were you a year ago?" was spoken by an adult male, digitized at the rate of 10 kHz, and analyzed in sampled-data format. Frequency and amplitude values were derived every 15 msec for the center frequencies of the first three formants by the method of linear predictive coding (LPC) (*2*). These values were hand-smoothed in some portions to ensure continuity and were used as synthesis parameters for a digital sine wave synthesizer. Three time-varying sinusoids were then generated to match the LPC-derived center frequencies and amplitudes of the first three formants, respectively, of the natural utterance. Figure 1 shows narrowband and wideband spectrograms of the original utterance and a narrowband spectrogram of its replica formed by the three time-varying sinusoids.

Although our synthetic stimuli were designed to preserve the frequency and amplitude variation of natural speech formants, the three-tone patterns differ from natural speech in several prominent ways. First, the energy spectra of the tones differ greatly from those of natural and synthetic speech. Voiced speech sounds, produced by pulsed laryngeal excitation of the supralaryngeal cavities, exhibit a characteristic spectrum of harmonically related values (*3, 4*). Because the frequencies of the individual tones in our stimuli follow the formant center frequencies, the components of the spectrum at any moment are not necessarily related as harmonics of a common fundamental. In essence, the three-tone pattern does not consist of harmonic spectra, although natural voiced speech does.

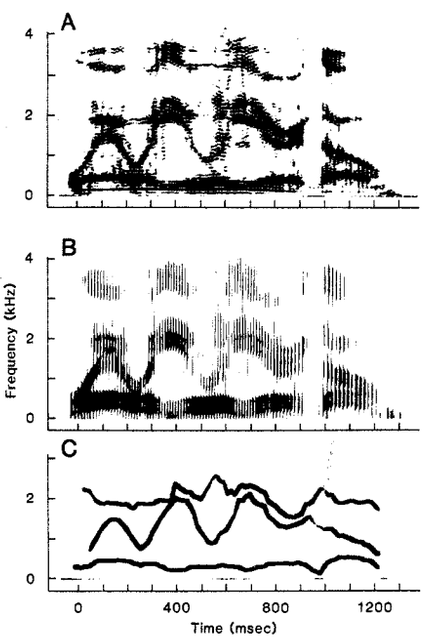

Fig. 1. (A) Narrowband spectrogram of the natural utterance "Where were you a year ago?" showing harmonic structure as narrow horizontal lines along the frequency scale. (B) Wideband spectrogram of the same utterance, showing formant pattern as dark bands along the time axis. The vertical striations correspond to individual laryngeal pulses. (C) Narrowband spectrogram of the three-tone sinusoidal replica. The energy concentrations follow the time-varying pattern of the formants above, but no energy is present except at the formant center frequencies. The amplitude variation in the sinusoidal pattern is not reproduced accurately.

Second, the short-time spectra of the tone stimuli lack the broadband formant structure that is also characteristic of speech (including whispered speech). Because the resonant properties of the supralaryngeal vocal tract introduce short-time amplitude maxima and minima across the harmonic spectrum of energy generated at the larynx, some frequency regions contain harmonics with more energy than neighboring regions (*5*). Our tone stimuli consist of no more than three sinusoids, so no energy is present in the spectrum except at the particular frequencies of each tone. Thus, the short-time spectra of the tone stimuli are also distinct in this way from the energy spectra of natural speech. There is no formant structure to the three-tone complexes, although the tones do exhibit acoustic energy at frequencies identical to the center frequencies of the formants of the original, natural utterance.

Third, the dynamic spectral properties of speech and tone stimuli are quite different. Across phonetic segments, the relative energy of each of the harmonics of the speech spectrum changes. Formant center frequencies may be computed by following the changes in amplitude maxima of the harmonic spectrum. However, natural speech signals do not exhibit continuous variation in formant frequency. Rather, laryngeal activity in voiced speech creates distinct pulses characterized by a formant structure. Thus, changes in formant structure, particularly when observed in wideband spectrograms, may erroneously appear to contain continuous formant variation over time. Figure 1B displays a wideband spectrogram in which the fine-grained amplitude differences are averaged over frequency to derive the formant pattern. In contrast to the case in speech, each tone in our stimuli continuously follows the computed peak of a changing resonance of the natural utter-

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